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A trial of thyroxine in acute renal failure

CHRISTOPHER G. ACKER, ASIM R. SINGH, RICHARD P. FLICK, JUDITH BERNARDINI, ARTHUR GREENBERG, and JOHN P. JOHNSON

Renal-Electrolyte Division, Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

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Background. Acute renal failure (ARF) remains a serious medical problem with a high mortality rate. Efforts to shorten the course of ARF might reduce this mortality. Since thyroxine has been shown in experimental models to shorten the course of ARF, we designed a trial to determine if a defined course of thyroxine would alter the course or change the mortality of clinical ARF.

Methods. A prospective, randomized, placebo-controlled, double-blind trial of thyroxine was carried out in patients with ARF. End points were the percentage requiring dialysis, the percentage recovering renal function, time to recovery, and mortality.

Results. Fifty-nine patients were randomized to receive either thyroxine or placebo. The groups were well matched in terms of basal and entry creatinines, age, sex, APACHE II scores at entry, and percentage oliguric. Baseline thyroid functions, including T_3, T_4, rT_3, and thyroid stimulating hormone (TSH) levels, were equal between the two groups and typical of patients with euthyroid sick syndrome. Thyroxine resulted in a progressive and sustained suppression of TSH levels in the treated group, but had no effect on any measure of ARF severity. Mortality was higher in the thyroxine group than the control group (43 vs. 13%) and correlated with suppression of TSH.

Conclusions. In contrast to the beneficial effects seen in experimental ARF, thyroxine has no effect on the course of clinical ARF and could have a negative effect on outcome through prolonged suppression of TSH. Critically ill euthyroid sick patients should not be replaced with thyroid hormone.

Acute renal failure (ARF) is a serious medical problem. Despite decades of improvement in supportive care, the mortality of ARF in the hospitalized acutely ill patient has changed little [1–3]. In contrast to this clinical picture, work in experimental ARF has suggested several promising therapeutic maneuvers, some of which have resulted in the amelioration or reversal of ischemic or toxic ARF in animal models. A number of growth factors, including insulin-like growth factor [4], epidermal growth factor [5], and hepatocyte growth factor [6], have been shown to enhance the recovery of renal function or to improve the survival in ischemic ARF in animals. Atrial natriuretic peptide has also been shown to be protective in experimental ARF [7, 8]. Several of these agents have subsequently been used in clinical trials but have not proved successful in altering the course of ARF in patients, as they were in experimental models [9–12].

The administration of thyroid hormone following initiation of ARF has been shown to be effective in promoting recovery from ARF in a wide variety of ischemic and toxic models of ARF [13–17]. Following renal injury, thyroid hormone was administered either as a single dose or over short time courses at amounts ranging from two to five times the normal replacement doses. Neither clinical nor laboratory evidence of hyperthyroidism was evident in treated animals. An uncontrolled clinical trial of thyroxine in a pediatric population reported that all patients diuresed following therapy [18]. Although thyroid hormone has not been tried in clinical ARF in adult patients, several trials have reported on the use of thyroid replacement in acutely ill patients [19–21]. The results of trials of thyroid hormone in the severely ill have not demonstrated a major improvement in morbidity nor mortality in relatively small groups. The studies have also not been able to show significant evidence of major adverse effects with the use of thyroid hormone in severely ill medical or surgical euthyroid patients. We therefore undertook a prospective randomized trial of thyroid hormone in the treatment of ARF to determine whether thyroid hormone altered the course or mortality associated with ARF.

METHODS

The study was designed as a prospective, randomized, double-blind trial of thyroxine in clinical ARF. ARF was defined as a doubling of serum creatinine within a 24-hour period. Exclusion criteria included: (*a*) evidence of reversible prerenal azotemia, defined as a fall in serum creatinine with correction of prerenal factors, (*b*) renal

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failure caused by urinary obstruction, (*c*) ARF secondary to acute glomerulonephritis or acute interstitial nephritis, (*d*) obstetrically related ARF, (*e*) patients with clinical evidence of hepatorenal syndrome, and (*f*) patients with unacceptable cardiac risk, defined as New York Heart Class IV [22]. Patients could be removed from the study if they developed chest pain suggestive of coronary ischemia, documented myocardial infarction, cardiac arrhythmia associated with circulatory compromise, or evidence of allergy to the study drug. No patients were withdrawn from the study for any of these criteria. All patients were examined prior to the entrance in the study and appeared to be clinically euthyroid. The study was approved by the Institutional Review Board for Biomedical Research at the University of Pittsburgh (Pittsburgh, PA, USA). Informed consent was obtained for all patients participating in the study.

Patients were randomly assigned to receive intravenous thyroxine (thyroid) or placebo (control); investigators were blinded to the group assignment. The protocol solution consisted of 150 μg of thyroxine in 20 mL of normal saline administered over five minutes by slow intravenous infusion. The placebo solution consisted of 20 mL of normal saline. Solutions were administered every 12 hours for 48 consecutive hours. The groups were treated and monitored in the intensive care unit (ICU). At entry, demographic data, major diagnoses, APACHE II score [23, 24], and presence or absence of oliguria (defined as urine output <400 mL/24 hours) were documented. Thyroid function studies [thyroid-stimulating hormone (TSH), free T_3, free T_4, and reverse T_3 (rT_3)] were obtained at study entry and on days 1, 7, and 14 after study entry.

End points of the study were patient mortality and severity of renal failure. These were initially examined separately because of the possibility that thyroid might affect one but not the other. Patients were followed until death or discharge from the hospital. To determine if there was a survival advantage, the percentage of survival for thyroid and control groups was compared using chi-square analysis with Yates correction. To examine the effect of thyroid on the clinical course of ARF, five measures of ARF severity were analyzed: (*a*) the percent requiring dialysis, (*b*) the percent recovering renal function, (*c*) the increase in serum creatinine concentration from baseline, (*d*) the time from initiation of ARF to earliest recovery (defined as increased urinary output or decline in creatine without dialysis), and (*e*) the time from initiation of ARF to stable recovery. Differences in the thyroid hormone measurements in the two groups over time were analyzed by analysis of variance supplemented by a one degree of freedom *t*-test if the significance was found by analysis of variance (ANOVA). Stepwise logistic regression was carried out with survival as the dependent variable. Predictors entered stepwise were age, sex, comorbid conditions (APACHE II), baseline creatinine concentration, presence of oliguria, thyroid function studies, and treatment group assignment (thyroid or control).

Table 1. Demographic and entry characteristics

	Control	Thyroid
N	31	28
Age *years*	58.5 ± 2.3	53.5 ± 3
% Male	61	58
APACHE II	17 ± 0.9	18 ± 1.4
% Oliguric	61	61
Creatinine (baseline)	1.1 ± 0.1	1.3 ± 0.1
Creatinine (entry)	3.8 ± 0.3	3.2 ± 0.3

Data are means ± SEM. There were no significant differences between the two groups.

All patients were evaluated by the same group of nephrologists at the University of Pittsburgh Medical Center (UPMC), and dialysis support was initiated for standard indications in the setting of ARF at this institution as previously described [25]. Renal replacement therapy was either intermittent hemodialysis (HD) performed with modified cellulose dialyzers, either cellulose acetate or hemophane, or continuous venovenous HD (CVVDH) using polyacrilonitrile dialyzers. The choice of dialysis mode was made on clinical grounds, and CVVHD was primarily used for those patients who required pressor support. Some patients received both modes.

Initial power analysis was carried out to ensure sufficient power to detect differences between treatment groups. Because the course of renal failure might be influenced with or without an effect on mortality, we assumed that mortality was the least sensitive while also the most reproducible outcome measure of ARF, and we used this outcome for the analysis. Because a retrospective study at our institution gave an overall mortality of 60% for ICU-acquired ARF [25], the study plan was to conduct a two-sided test to determine a 33% difference in mortality (that is, a decrease in mortality to 40%). The chi-squared test for comparing two binomial proportions was used for the analysis. The sample size determined called for 97 subjects per group [26]. During the trial, the mortality response was monitored for early dramatic benefits or potential harmful effects, using the sequential method of Pocock [27]. The test statistic was computed following data acquisition of the first 60 subjects, without breaking the code by the investigators. Because a significant difference in mortality was observed at the first analysis, the trial was terminated.

RESULTS

Entry characteristics for the thyroid and control groups are shown in Table 1. The groups were similar in age, sex, APACHE II scores at enrollment, the percentage

Table 2. Etiologies of acute renal failure (ARF)

	Control	Thyroid
Toxic	6	9
Ischemia + sepsis	8	6
Ischemia without sepsis	17	13

The most likely primary etiology for ARF was estimated by clinical evaluation of presentation. Toxic included antibiotic (primarily aminoglycoside), NSAID toxicity, rhabdomyolysis, and radiocontrast agents. Hypotension (ischemia) was divided by whether or not it occurred in the presence of presumed sepsis. There was no difference in frequencies of etiologies between the two groups.

who were oliguric, and entry and baseline serum creatinine values. Consistent with our previous observations at this institution [25], the majority of patients in both groups received total parenteral nutrition (TPN) during their stay in ICU, and the use of TPN was not different between the two groups (data not shown). Etiologies of ARF, determined during clinical evaluation of the patients as the most likely primary cause of ARF, are listed in Table 2 for the two groups. There was no significant difference between the two groups in terms of the distribution of major etiologic events for ARF. The thyroid function tests of the two groups are shown in Table 3. At the beginning of the study (day 0), all patients showed the same pattern of low T_4, low normal TSH levels, and elevated rT_3 levels typical of the euthyroid sick syndrome [28]. There were no significant differences in any of these measures between the two groups at the start of the study. The only significant changes in these measures during the course of the study were a fall in TSH levels in the thyroid group at days 1 and 7, and a rise in TSH levels in the control group throughout the study period. The TSH level was significantly greater in control compared with the thyroid group at day 7.

Outcomes of the two groups are shown in Table 4. There was no significant difference between thyroid and control groups in any measure of severity of ARF. The percentage requiring dialysis, time on dialysis, time to earliest and stable recovery, and percentage of recovering function were similar in both groups. There was a significant difference in mortality between the two groups. Mortality was significantly higher in the thyroid group. The mean time from entry to death for those who died was not different between the two groups.

Stepwise regression analysis was undertaken to determine which clinical or laboratory characteristics best correlated with mortality. Neither age, sex, APACHE II score, need for dialysis, creatinine at entry, presence of oliguria, or group assignment (thyroid or control) correlated significantly with survival. The only significant relationship to outcome was with TSH level at day 1 of the trial. We therefore examined the relationship between TSH level and survival in more detail. Table 5 demonstrates the TSH levels for survivors and nonsurvivors at all points measured for both groups. TSH was higher in survivors than nonsurvivors throughout the study and was significantly higher for survivors in both groups at day 1. This relationship becomes clearer when all patients are viewed together, irrespective of group assignment (Fig. 1). The TSH level in survivors was significantly higher than in nonsurvivors at entry into the study and progressively rose throughout the study. TSH levels for nonsurvivors remained quite low throughout the study. In an attempt to characterize this potentially important marker further, we also compared survivors with nonsurvivors in terms of clinical factors (Table 6). Survivors tended to be younger, have lower APACHE II scores, be less frequently oliguric, and have a less frequent requirement for dialysis than nonsurvivors. However, none of these differences reached statistical significance. Consistent with the results of the regression analysis, TSH at day 1 was the most robust discriminator between survival and death.

Steroid and dopamine use have been reported to influence thyroid economy in critically ill patients [28, 29]. We therefore examined steroid and dopamine usage in both groups within 48 hours prior to and following study entry. Steroid and dopamine usage were similar for both groups (control 71.7%, thyroid 57.1%, P = NS). We also compared steroid and dopamine use between survivors (with rising TSH levels) and nonsurvivors (with low TSH levels). The use of steroids and dopamine within 48 hours prior to and following study entry was similar between survivors and nonsurvivors (Table 6). There were no differences between the two groups.

DISCUSSION

Thyroid hormone (either T_3 or T_4) has been shown to be active in promoting recovery from ARF in a wide variety of animal models [13–17]. A single, uncontrolled trial in children suggested promising results [18]. Several studies report the use of thyroid hormone in adults in ICU settings with acute nonthyroidal illness [19–21]. These studies were prompted by a considerable body of clinical observations suggesting abnormalities in the thyroid axis of the acutely ill, which have been characterized as the euthyroid sick syndrome [28]. The hallmarks of this syndrome are low T_3, low to normal T_4, elevated rT_3, and normal TSH. The significance of these findings to outcome in severely ill patients is conjectural. Although apparently euthyroid by clinical measures, the notion that these patients are truly euthyroid has been questioned [30]. The value of thyroid hormone replacement remains unknown [30–32], but the studies so far performed in non-ARF patients have not shown a significant effect on outcome, either positive or negative, in critically ill adults. Our study demonstrates that patients with ARF exhibit biochemical findings typical of the euthyroid sick syndrome. Thyroid replacement in this

Table 3. Thyroid hormone results

	TSH (0.272–5.39 mU/mL)		FT_4 (0.76–1.79 ng/dL)		FT_3 (1.90–5.00 pg/mL)		rT_3 (80–350 ng/L)	
Day	T_4Rx	Control	T_4Rx	Control	T_4Rx	Control	T_4Rx	Control
0	089 ± 0.35	1.09 ± 0.31	0.73 ± 0.10	0.71 ± 0.03	2.49 ± 1.55	0.84 ± 0.05	652.32 ± 151.74	1028.37 ± 325.03
1	0.81 ± 0.40	1.42 ± 0.46	0.88 ± 0.10	0.73 ± 0.043	1.07 ± 0.20	0.90 ± 0.15	658.26 ± 210.78	909.5 ± 391.07
7	0.87 ± 0.23[a]	2.75 ± 0.62[b]	0.71 ± 0.06	0.66 ± 0.04	0.96 ± 0.11	0.94 ± 1.10	NA	NA
14	2.14 ± 0.81	3.42 ± 0.59[b]	0.77 ± 0.07	0.78 ± 0.06	1.09 ± 0.17	1.13 ± 0.22	NA	NA

Values are given as mean ± SEM.
Abbreviations are: TSH, thyroid stimulating hormone; FT_4, free T_4; FT_3, free T_3; rT_3, reverse T_3; NA, not assessed; T_4Rx is patients treated with thyroxine.
[a] $P = 0.01$ T_4Rx vs. control
[b] $P = 0.02$ Control day 0 vs. days 7, 14

Table 4. Outcomes

	T_4Rx ($N = 28$)	Control ($N = 31$)
S_{Cr} (peak)	5.3 ± 0.5	4.6 ± 0.5
S_{Cr} (recovery)	1.6 ± 0.2	1.5 ± 0.1
Required dialysis %	64.00	48.00
HD %	28.5	26.0
CVVHD %	10.5	3.0
Both %	25.0	19.0
Time on dialysis *days*	16 ± 7	11 ± 4
Time/R1 *days*	9 ± 4	9 ± 3
Time/R2 *days*	16 ± 4	14 ± 3
Recovery of function	15/28	20/31
Mortality	12 (43%)[a]	4 (13%)
Time (entry to death) *days*	15 ± 4	16 ± 12

Abbreviations are: S_{Cr} (peak), maximal creatinine value; S_{Cr} (recovery), creatinine level at renal recovery; Time/R1, time to initial decline in serum creatinine; Time/R2, time to stable creatinine level. Individual modalities of dialysis support are presented as % of total group and sum to equal overall % requiring any dialysis.
[a] $P = 0.01$ by Fisher's exact test

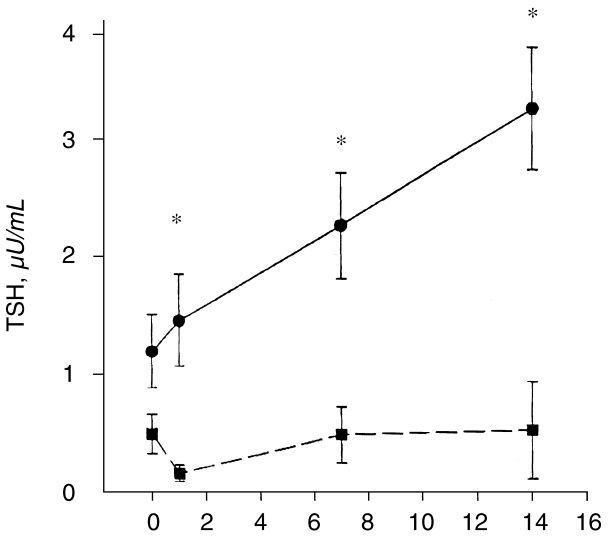

Fig. 1. Comparison of thyroid stimulating hormone (TSH) levels between survivors (●) and nonsurvivors (■) irrespective of the group assignment. TSH levels were significantly higher in survivors at day 1, 7, and 14. Values are presented as mean ± SEM, $P < 0.05$.

Table 5. TSH (μU/mL) for survivors and non-survivors

	Control		T4Rx	
Day	Survivors	Non-survivors	Survivors	Non-survivors
0	1.13 ± 0.35	0.83 ± 0.58	1.32 ± 0.63[a]	0.37 ± 0.10
1	1.53 ± 0.49[a]	0.02 ± 0.00	1.32 ± 0.69[a]	0.19 ± 0.08
7	2.97 ± 0.65	0.39 ± 0.00	1.06 ± 0.30	0.52 ± 0.31
14	3.59 ± 0.60	0.36 ± 0.00	2.61 ± 1.00	0.58 ± 0.58

[a] $P < 0.03$ survivors vs. non-survivors

Table 6. Characteristics of survivors and non-survivors

	Survivors ($N = 43$)	Non-survivors ($N = 16$)
Age	53.9 ± 2.5	60.4 ± 3.5
APACHE II	17.4 ± 1.08	19.5 ± 1.65
% Oliguric	57	69
% Dialysis	44	68
Dopamine use %	48	60
Steroid use	30%	31%

Data are shown as mean ± SEM or % of total per group. There were no significant differences between groups in these parameters.

euthyroid sick state in patients similarly matched for age, severity of disease, and level of renal dysfunction appears to result in a continued suppression of TSH, as control patients exhibited a progressive rise in TSH throughout the study period. Although no other clinical or biochemical evidence of hyperthyroidism was noted in our population, the continued suppression of TSH correlated with the poorer outcome for thyroid treated patients clearly indicates that euthyroid sick patients should not be replaced with thyroid hormone.

In contrast to the remarkable effects of thyroxine on experimental ARF, no effect on renal function or renal recovery was observed in our patient population. Although the numbers are small in this study, there was no hint of an effect of renal failure. Along with insulin-like growth factor-1 (IGF-1) [10] and atrial natriuretic peptide (ANP) [9, 12], this represents the third agent that showed great promise in laboratory ARF but little effect in clinical ARF. The possible reasons for this have

recently been discussed [11, 33]. This study relied on changes in serum creatinine and clinical maneuvers to rule out prerenal states to identify true ARF. As a result, renal failure was established and relatively severe by the time therapy was begun. The serum creatinine was more than double the baseline values at the time of entry into the study. These facts alone are not necessarily inconsistent with the rationale for thyroid hormone in ARF, as it has been shown that thyroid is effective only after the insult that induces ARF and remains effective for up to 24 hours after the initiation of ARF [13, 16]. It is possible, however, that the ARF in experimental models, generally recoverable without other interventions, may have been milder and therefore more likely to respond to intervention than that seen in the clinical setting. In addition, there may be confounding effects of the complicated clinical course on ARF outcomes that would obscure any positive effect of the intervention, such as recurrent hypotension, secondary insults related to drugs, or even dialysis. In this regard, there is no way in which a pure laboratory model of ARF can reproduce the complex situation of clinical ARF in the ICU patient. This complexity raises the possibility that agents that are benign and even helpful in the experimental condition may have untoward effects when applied in the clinical setting.

This study was terminated at its earliest data calculation point because a difference in mortality was noted between the two groups. Mortality in the control group was 13%, and in the thyroid group, mortality was 43%. The observed mortality in controls in this study was less than that typically seen at our institution [25] in ARF in ICU patients, whereas the 43% mortality noted in the thyroid group better approximates both our experience and that reported in the literature for ICU patients [34]. It is possible that extremely ill patients were withheld from the study by their primary physicians, as APACHE II scores tended to be somewhat lower than those described in our previous study [25]. Although this might help explain the observed lower mortality in the control group, it cannot explain the differences in outcome between the two groups because they were comparable in APACHE II scores at study entry. The time from study entry to death, for those patients who died, was several weeks and was not different between the two groups. There was no evidence of an acute effect of thyroid hormone in the treated group in terms of direct actions of thyroid hormone. These observations lead us to question whether the mortality in the thyroid group should be attributed solely to thyroxine therapy. Nevertheless, the significant suppression of TSH seen at day 7 in the thyroid group, coupled with the strong correlation between mortality and continued TSH suppression in all patients, suggests that there may be a cause and effect association. Studies of agents thought to be effective in ARF ultimately require human trials that inevitably take place in circumstances considerably more complex than experimental models. Our experience underscores the need to conduct such trials with early and frequent monitoring of outcomes. Finally, our results suggest that derangements in the thyroidal axis in critical illness may help to predict eventual patient outcome. Sustained suppression of TSH may identify a group of patients with increased mortality [35].

Reprint requests to John P. Johnson, M.D., 935 Scaife Hall, 3550 Terrace Street, Pittsburgh, Pennsylvania 15213, USA.

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